State of California
M e m o r a n d u m

HSM-94007
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To: John Inouye, Registration Specialist
Pesticide Registration Branch

Date: February 25, 1994

Place: Sacramento

4-0455

From: Department of Pesticide Regulation -Tom Thongsinthusak, Staff Toxicologist
Worker Health and Safety Branch

Subject: PRODUCT NAME: Guthion
ACTIVE INGREDIENT: Azinphos-methyl
COMPANY NAME: Mobay Chemical Corp.
I.D. NUMBER: SBRA-133980-E
DOCUMENT NUMBER: 154-261
EPA REGISTRATION NUMBER: 3125-0-
TITLE: Guthion: Dermal Absorption Study

A dermal absorption study of azinphos-methyl (Guthion) in male rats was conducted by Miles, Inc. This study was performed according to the study protocol which was reviewed and commented on by the Worker Health and Safety Branch, Department of Pesticide Regulation. The study was also conducted in compliance with Good Laboratory Practice standards. The Quality Assurance officer inspected various phases of the study and signed the final report. A summary of this dermal absorption study and the evaluation of the results are presented below.

A. Preparation of Animals

Adult male Sprague-Dawley derived rats (*Rattus norvegicus*) were used in this dermal absorption study. Body weights of these rats ranged from 202 to 275 grams. These animals were inspected and acclimatized prior to the study. The room temperature was set at 65 to 78 ^{o}F with 40 to 70% relative humidity. The photo period was 12 hours of light/12 hours of dark cycle. Approximately one day prior to the study, the backs of animals were clipped with electric clippers and the clipped areas were washed with acetone.

B. Administration of the Doses

Three dose levels and untreated and sham-treated controls were used in this study. The dose was prepared by adding the appropriate amounts of high purity [phenyl-UL-^{14}C] azinphos-methyl (99.3% pure) and non-labeled azinphos-methyl to a blank Guthion formulation (35% WP) and suspended in deionized water. The dose solution was applied at a volume of 150 uL per 15 cm^2 of treated skin site. The nominal doses were 56, 560, and 5,600 ug of azinphos-methyl/kg body weight equivalent to 0.93, 9.3, and 93 ug azinphos-methyl/cm^2. Four animals were used per sacrifice time of each dose. After administration of the test material, the treated skin sites were protected with a nonocclusive cover made with a rubber ring (5.0 cm ID) and filter paper.

[original signed by T. Thongsinthusak]

Protective collars were used to restrict movement of animals from accessing the treated skin sites. The animals were housed individually during the study in stainless steel cages that allowed collection of urine and feces samples.

C. Sample Collection and Analysis

The sacrifice times for various groups of animals were: 1, 4, 10, 24, 72 and 168 hours. For the 24, 72 and 168-hour sacrifice times, treated skin sites were lightly wiped twice with gauze pads moistened with a 5% aqueous detergent (Contrad 70) solution and once with a dry gauze pad ten hours after exposure. These animals were returned to their cages for further monitoring. Daily urine and feces samples were collected and analyzed separately. Samples collected for analysis were: application device, nonocclusive cover, skin wash, treated skin site, cage wash, blood, carcasses, feces, and urine.

D. Determination of the Results

Recovery of administered doses of azinphos-methyl for the 1, 4, 10, and 168-hour sacrifice times are shown in Table 1. The results of the study indicated that dermal absorption of azinphos-methyl is dose dependent, i.e. percent dose absorbed for the low dose is higher than that for the medium and high doses. Furthermore, percent dose absorbed is greater for the longer exposure and sacrifice times for the same dose level. The highest percent dose in the treated skin site was 36.44% at 1-hour sacrifice time for the low dose, whereas, for medium and high doses were 22.08 and 23.71% 10 hours after dosing, respectively.

Excretion kinetics of azinphos-methyl in urine and feces from treated animals were observed over 168 hours after dosing. Percent of dose excreted at different time intervals were tabulated (Table 2). Excretion of the dose for the 24 and 72-hour sacrifice times for all dose groups were similar to those with the same sample collection times for the 168-hour sacrifice time. This indicated a consistency in study procedures and the analysis of samples.

In order to resolve the issue of bound skin residue, cumulative percent doses in urine and feces for different time intervals extrapolated beyond 168 hours were used for estimating the asymptote by employing an exponential saturation model with lag time. An equation representing this model is: Y = A*(1-EXP(-B*(X+C))) or Recov = Max*(1-EXP(-Rate*(Time+Lag))). An example of the plots for the lowest dose and the outputs are shown in Figure 1. The dermal absorption value is the sum of percent dose at asymptote (maximum or "A" term) and percent of dose recovered in carcasses, blood, and cage washes. Table 3 summarizes the dermal absorption values for low, medium and high doses obtained from this study. The corrected dermal absorption values for the lowest dose (0.93 ug/cm^2) with 10-hour exposure time is appropriate to be used in the exposure

estimates because this dose should be representative of exposure experienced by agricultural workers.

Plasma and erythrocyte cholinesterase levels in test animals were also determined in this study. For all dose groups, azinphos-methyl did not result in a plasma or erythrocyte cholinesterase depression that exceeded 20% of the control level. However, a dose of 93 ug/cm^2 caused erythrocyte cholinesterase depression ranging from 9 to 17% compared to a control group.

Recommendations:

1. The dermal absorption study of azinphos-methyl in male rats as reported in document number 154-261 is acceptable.

2. Dermal absorption of 44.2 percent may be used to estimate absorbed dosages of persons exposed to azinphos-methyl unless human dermal absorption data is available.

cc: Joshua Johnson (1 original, 5 copies)
John Ross
Tareq Formoli

Table 1. Recovery of administered dose of azinphos-methyl.

	Percent dose (mean)								
Dose (a.i.)	Sacrifice time (h)	Unab-sorbed*a	Treated skin site	Blood	Urine	Feces	Carcass	Cage wash	Total recovery
0.84 ug/cm2	1	55.53	36.44	0.17	0.34	0.04	8.78	0.08	101.38
(0.93 ug/cm2)*b			(1-h) Absorbed dose (%dose)*c =			45.85			
	4	52.72	25.78	0.43	2.37	0.31	19.55	0.37	101.53
			(4-h) Absorbed dose (%dose)*c =			48.81			
	10	48.26	32.24	0.36	4.86	0.38	16.44	0.66	103.2
			(10-h) Absorbed dose (%dose)*c =			54.94			
	168	39.98	15.82	0.08	26.24	9.8	1.87	3.65	97.44
8.78 ug/cm2	1	58.41	19.16	0.05	0.14	0.01	3.43	0.04	81.24
(9.3 ug/cm2)*b			(1-h) Absorbed dose (%dose)*c =			22.83			
	4	60.13	21.57	0.06	0.34	0.04	4.32	0.14	86.6
			(4-h) Absorbed dose (%dose)*c =			26.47			
	10	46.31	22.08	0.22	2.82	0.36	11.19	0.57	83.55
			(10-h) Absorbed dose (%dose)*c =			37.24			
	168	53.77	5.43	0.04	11.77	5.83	1.64	2.57	81.05
98.7 ug/cm2	1	76.06	19.74	0.01	0.02	0	0.45	0	96.28
(93.0 ug/cm2)*b			(1-h) Absorbed dose (%dose)*c =			20.22			
	4	78.72	14.61	0.02	0.14	0.01	1.08	0.02	94.6
			(4-h) Absorbed dose (%dose)*c =			15.88			
	10	68.91	23.71	0.04	0.63	0.02	2.12	0.05	95.48
			(10-h) Absorbed dose (%dose)*c =			26.57			
	168	67.41	7.06	0.03	10.14	5.07	1.33	1.76	92.8

*a Protective cover + ring wash + skin wash

*b Nominal dose

*c When bioavailability of bound skin residues cannot be determined, dermal absorption values = % dose recovered from treated skin site + blood + urine + feces + carcass + cage wash.

(TXL/Dermal/Guthion1)

Table 2. Percent dose of azinphos-methyl excreted following 10-hour exposure.

A. Actual dose: 0.84 ug/cm2

	Percent dose (mean)				
Time (h)	Urine (U)	Feces (F)	U + F		Cumulative
24	15	2.7	17.7		17.7
48	4.9	3.6	8.5		26.2
72	1.4	1	2.4		28.6
96	1.9	1.2	3.1		31.7
120	2	1.2	3.2		34.9
144	1.2	0.6	1.8		36.7
168	1	0.6	1.6		38.3
Total	27.4	10.9	38.3		

B. Actual dose: 8.78 ug/cm2

	Percent dose (mean)				
Time (h)	Urine (U)	Feces (F)	U + F		Cumulative
24	6.7	1.5	8.2		8.2
48	3.1	1.6	4.7		12.9
72	1.1	0.6	1.7		14.6
96	0.3	0.2	0.5		15.1
120	0.6	0.4	1		16.1
144	0.8	0.4	1.2		17.3
168	0.9	0.7	1.6		18.9
Total	13.5	5.4	18.9		

C. Actual dose: 98.7 ug/cm2

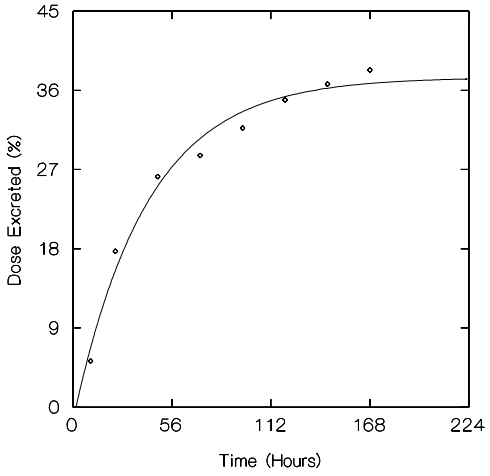
	Percent dose (mean)				
Time (h)	Urine (U)	Feces (F)	U + F		Cumulative
24	2.3	0.5	2.8		2.8
48	2	1.1	3.1		5.9
72	1.2	0.8	2		7.9
96	1.1	0.6	1.7		9.6
120	1	0.5	1.5		11.1
144	0.8	0.5	1.3		12.4
168	0.7	0.5	1.2		13.6
Total	9.1	4.5	13.6		

Table 3. Summary: Dermal absorption of azinphos-methyl in male rats*a.

Actual dose	Nominal dose		Percent dose (mean)					
(ug/cm2)	(ug/cm2)	Excreted*b	Blood	Carcass	Cage wash	Sub-total	Recovery	Adj. total
0.84	0.93	37.5	0.08	1.87	3.65	43.1	97.44	44.23
8.78	9.3	14.7	0.04	1.64	2.57	18.95	81.05	23.38
98.7	93	17.4	0.03	1.33	1.76	20.52	92.8	22.11

*a Percent doses: excreted + blood + carcass + cage wash.
*b At asymptote using an exponential saturation model.
(TXL\Dermal\Guthion2)

Figure 1. Azinphos-methyl: Asymptotic plot of cumulative excretion of dose in urine and feces at different time intervals for 0.84 ug/cm^2

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>NONLIN
>MODEL RECOV=Max*(1-Exp(-Rate*(Time+Lag)))
>ESTIMATE/ QUASI

WED 2/23/94 9:30:35 AM   C:\TCSYS\GUTHION1.SYS

 ITERATION      LOSS      PARAMETER VALUES
    0      .6838779D+04 .1000D+00 .1000D+00 .1000D+00
    1      .8680116D+03 .2742D+02 .9789D+00 .1047D+00
    2      .8350973D+03 .2744D+02 .3579D+00 .4448D-01
    3      .6359906D+03 .2744D+02 .1569D+00 .3734D-01
    4      .3578665D+03 .2745D+02 .6488D-01 .3601D-01
    5      .3144805D+03 .2745D+02 .4349D-01 .3589D-01
    6      .8168787D+02 .3184D+02 .4752D-01-.6914D+01
    7      .5060506D+02 .3335D+02 .3415D-01-.5450D+01
    8      .2681820D+02 .3552D+02 .3242D-01-.5824D+01
    9      .2350264D+02 .3673D+02 .2440D-01-.3539D+01
   10      .1970548D+02 .3660D+02 .2634D-01-.3563D+01
   11      .1846508D+02 .3720D+02 .2522D-01-.2210D+01
   12      .1813839D+02 .3728D+02 .2456D-01-.2086D+01
   13      .1807941D+02 .3742D+02 .2392D-01-.1819D+01
   14      .1807333D+02 .3746D+02 .2388D-01-.1736D+01
   15      .1807267D+02 .3747D+02 .2385D-01-.1730D+01
   16      .1807267D+02 .3747D+02 .2385D-01-.1730D+01
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DEPENDENT VARIABLE IS RECOV

SOURCE	SUM-OF-SQUARES	DF	MEAN-SQUARE
REGRESSION	6863.759	3	2287.920
RESIDUAL	18.073	5	3.615
TOTAL	6881.828	8	
CORRECTED	868.073	7	

RAW R-SQUARED (1-RESIDUAL/TOTAL) = 0.997
CORRECTED R-SQUARED (1-RESIDUAL/CORRECTED) = 0.979

PARAMETER	ESTIMATE	A.S.E.	LOWER	<95%> UPPER
MAX	37.466	1.771	32.913	42.019
RATE	0.024	0.005	0.011	0.037
LAG	-1.730	3.430	-10.546	7.087

(TCW\Dermal\Guthion2)